REMARKS

Claims 28, 29, 31, 32 and 44-47 are pending. Claim 44 has been amended to clarify that FR4 is selected from a single third human antibody. Claims 28, 29, 31, 32 and 44-47 are presented for further consideration.

The rejection of claims 28, 29, 31, 32 and 44-47 are rejected under Section 102(a) based on Harris *et al.* (WO 94/09136, published 4/28/1994) has been maintained. Applicant previously forwarded a Rule 131 declaration of Dr. Hans Hansen, one of the inventors, which showed that applicant had reduced the present invention to practice prior to the effective date of the cited Harris document. In addition, applicant presented the declaration of Mr. Bryan Wilson, documenting attempts to obtain a similar declaration from Dr. Leung, the other co-inventor. Most recently, the undersigned submitted a declaration detailing further attempts to obtain Dr. Leung's signature. The examiner has indicated that "Applicant should resubmit the petition under 37 CFR 1.183 along with the evidence of refusal to sign provided in the most recent reply (filed 5/4/2011)." A renewed petition under 37 CFR 1.183 is being filed concurrently with the present response, along with a petition under 37 CFR 1.103 to suspend prosecution for 6 months, so that a decision on the petition under 37 CFR 1.183 can be rendered before the examiner takes up the RCE for further examination.

However, it is submitted that further petition should not be required in this case, since the undersigned now has provided an ultimatum as directed by the Petitions Branch which would support "a finding of refusal by conduct." Furthermore, it is noted that the requirement for Dr. Leung's signature on this declaration was waived in SN 11/676,466, which shares priority to the same parent case as the present case, the Petitions Examiner noting that "in the interest of justice, the signature requirement of Dr. Leung on the declaration under 37 CFR 1.131 is waived." Accordingly, the examiner should withdraw the rejection based on Harris *et al.* based on the current record.[1]

Claims 44-47 are rejected under Section 102(b) based on Adair *et al.* (WO 91/09967). The examiner cites Adair (WO 91/09967) as teaching a method of designing humanized heavy and light

[1] As previously noted, the declaration of Dr. Hansen is sufficient to establish prior reduction to practice of the presently claimed subject matter, thereby removing Harris as a reference. The examiner has not set forth any substantive basis for maintaining the rejection based on Harris, merely the procedural one based on the absence of Dr. Leung's declaration. Accordingly, no further comment is necessary on the part of applicant.

chain variable domain amino acid sequences of murine monoclonal antibody B72.3 comprising comparing the light and heavy chain variable domain sequences of B72.3 with the light and heavy chain sequences of two or more human antibodies (*e.g.*, those in Kabat), wherein the human REI light chain frameworks are selected and the human EU heavy chain frameworks are selected for FR1, FR2 and FR3 and a human consensus heavy chain FR4 was selected and the selected human frameworks are incorporated with the corresponding light and heavy chain CDRs of B72.3 and the light chain mouse residue at position 48 (2 amino acids from CDR2) and the heavy chain mouse residues at position 73, which is close to both CDRs 1 and 3 and could have a detrimental effect on antigen binding were retained in the humanized B72.3 antibody (*i.e.*, residues predicted to have contacts with the CDRs and within a 4.5 Angstrom radius of any atoms within the CDRs).

Claims 44-47 all recite "selecting framework regions from a first human antibody for the light chain and from second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from the third human antibody." The examiner admits in the statement of rejection that "the human REI light chain frameworks are selected and the human EU heavy chain frameworks are selected for FR1, FR2 and FR3 and a human consensus heavy chain FR4 was selected." Thus, even the examiner does not state that FR4 was selected from a third antibody, but rather that a "consensus" FR4 is selected. A consensus sequence refers to the most common nucleotide or amino acid at a particular position after multiple sequences are aligned, *i.e.,* it is a way of representing the results of a multiple sequence alignments, where related sequences are compared to each other. A consensus sequence cannot be "selected from a third antibody" as presently claimed.

In response to this explanation, the examiner urges that "Adair et al. teach selecting FR4 from a consensus sequence which would meet the limitations of being from an antibody other than the first and second antibodies." In order to clarify that the invention as recited in claim 44 is not merely that the sequence is from an antibody other than the first and second antibodies, claim 44 has been amended to more particularly recite that FR4 is selected from a single third human antibody. This clearly is supported by the specification (for example, by disclosure that "antibody EU (VH) sequences can be selected as the computer counterparts for FR1 to FR3 of the mLL2 heavy chain; FR4 was based on NEWM" and "The FR4 sequence of NEWM, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 heavy chain"). The consensus sequence of Adair clearly does not anticipate claims 44-47 as amended.

Adair did not compare the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized with the amino acid sequences of the light and heavy chain variable domains of two or more human antibodies, then select framework regions from a first human antibody for the light chain, and from second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from a single third human antibody, and then incorporate the framework regions selected with the corresponding light and heavy chain complementarity determining regions of the monoclonal antibody to be humanized, to design a humanized light and heavy chain variable domain amino acid sequences. Adair used a consensus FR4, and therefore does not teach "FR4 is selected from a single third human antibody" as presently claimed. On this basis alone, the rejection under Section 102 must fail.

If there are any problems with this response, or if the examiner believes that a telephone interview would advance the prosecution of the present application, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

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DATE

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